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Abdominal Ultrasound Findings Mimicking Hematological Malignancies in a Study of 218 Gaucher Patients

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Gaucher disease, the most prevalent sphingolipidosis, generally presents with splenomegaly, anemia, and thrombocytopenia. Hence, hematologists are often the specialists involved in diagnosis and management of these patients. We present ultrasonographic characteristics in a cohort of 218 consecutive Gaucher patients evaluated in our clinic during the past 5 years. Our data emphasize the high prevalence of lesions mimicking hematological malignancies in Gaucher disease. One fifth of 184 non-splenectomized patients had intra-splenic lesions, 6% of all patients had similar lesions in the liver, and 32% of 34 splenectomized patients (but none of the other patients) had marked retroperitoneal or peri-portal lymphadenopathy.

The presence of splenic lesions correlated with age and splenic size, but not with extent of bone involvement or genotype. Interestingly, they were not affected by reduction in splenomegaly following enzyme replacement therapy.

The importance of these findings is to include Gaucher disease in the differential diagnosis of splenic or hepatic lesions, especially in Ashkenazi Jews. Conversely, they are relevant for follow-up of all Gaucher patients, including asymptomatic individuals, because of the reported increased incidence of hematological malignancies in Gaucher disease. Am. J. Hematol. 55:28–34, 1997.

Key words: Gaucher disease; ultrasound; hematological malignancies; abdominal lymphadenopathy; enzyme replacement therapy

INTRODUCTION

Gaucher disease, the most prevalent sphingolipid storage disorder, is inherited as an autosomal recessive trait and is characterized by accumulation of the sphingolipid glucocerebroside in reticuloendothelial cells, including spleen, liver, and bones [1].

Splenomegaly is among the earliest signs of Gaucher disease and can be demonstrated on ultrasound even in cases where the spleen is not palpable [2]. In most symptomatic patients there is a degree of liver involvement, usually manifested as hepatomegaly. We herein describe the abdominal sonographic characteristics in a series of 218 consecutive Gaucher patients, evaluated at presentation in our clinic. We note a high prevalence of focal lesions in the spleen, liver, and in prominent accessory spleens. A novel finding of a high prevalence of abdominal lymphadenopathy in splenectomized patients is documented.

We discuss our findings in light of the reported increased incidence of hematological malignancies in Gaucher disease [3] and with relevance to the effects of enzyme replacement therapy [4,5].

PATIENTS AND METHODS

All patients who presented in our Gaucher clinic in the past 5 years (1991–1995) have undergone routine abdominal ultrasound examination for baseline evaluation including measurements of liver volume indices, which are the mathematical product of the three largest organ dimensions (longitudinal, transverse, and anterior-posterior) [6], as well as similar measurements of spleen volume indices. All examinations were performed using

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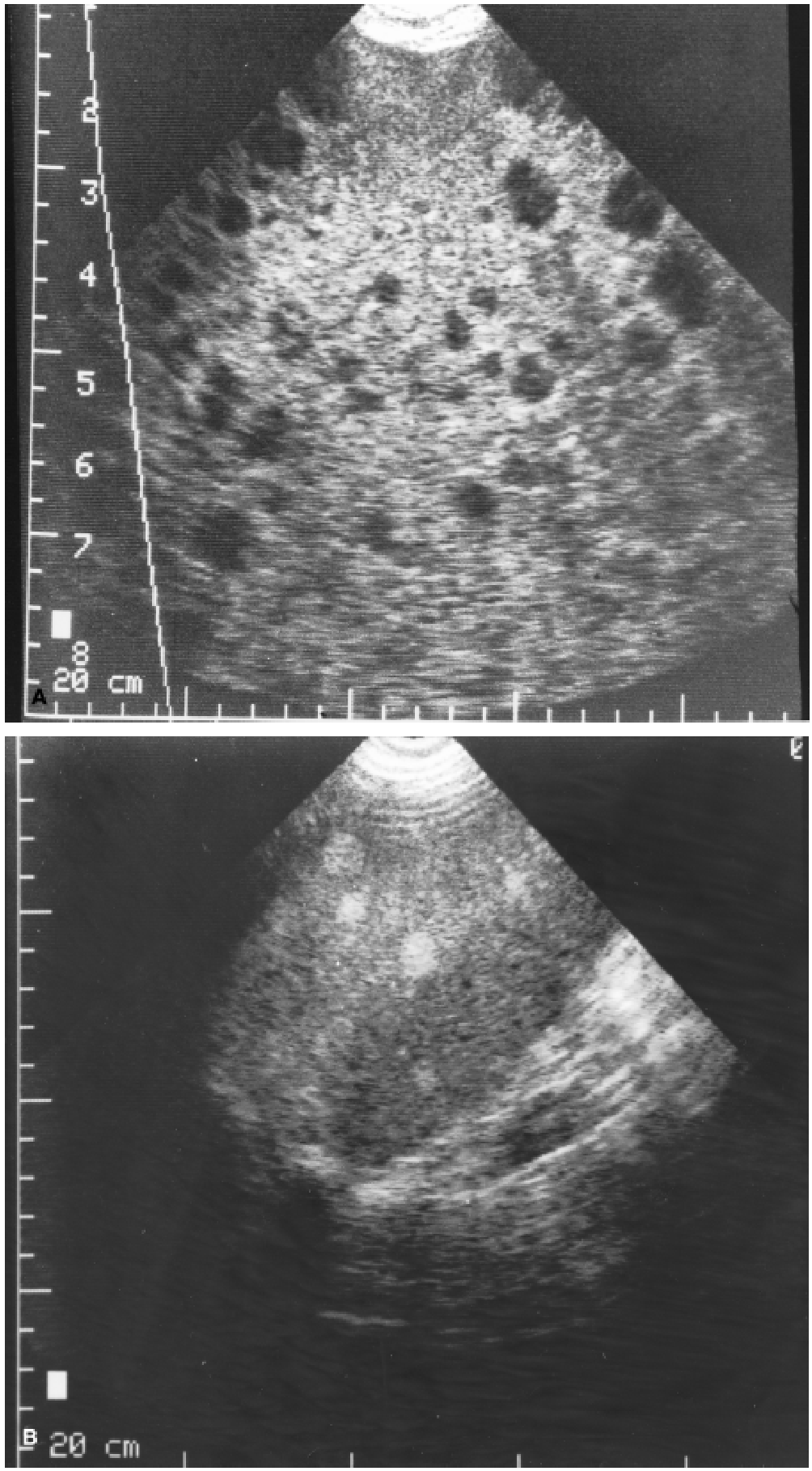

Fig. 1. Intrasplenic focal lesions. A: Multiple hypo-echoic lesions. B: Multiple hyper-echoic lesions. C: Three different lesions in the same spleen, a small hypo-echoic, a large non-homogenous hyper-echoic mixed, and a moderate-size mixed hypo-echoic lesion surrounded by hyper-echoic rim. (Figure continues on next page.)

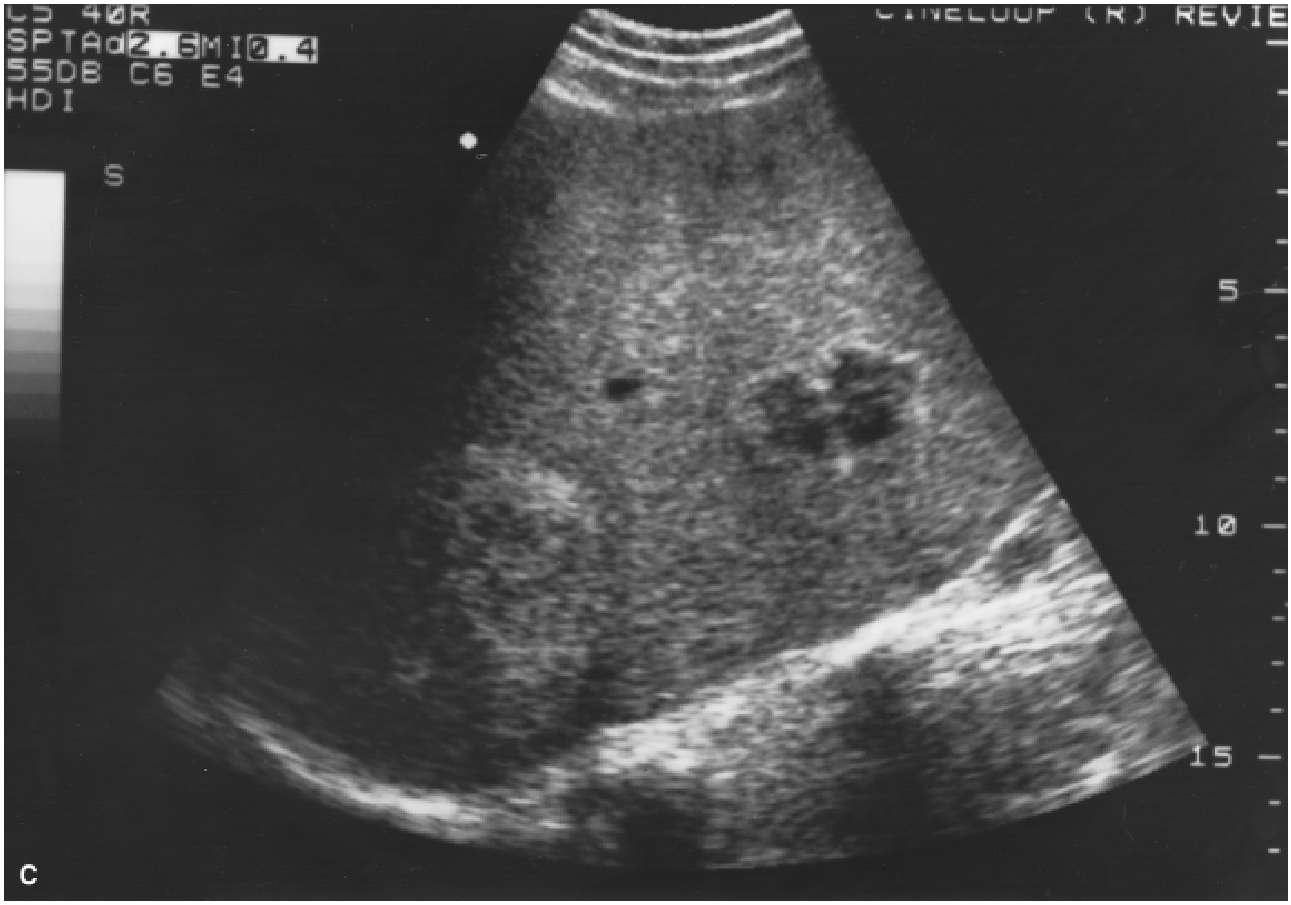

Fig. 1. (Continued).

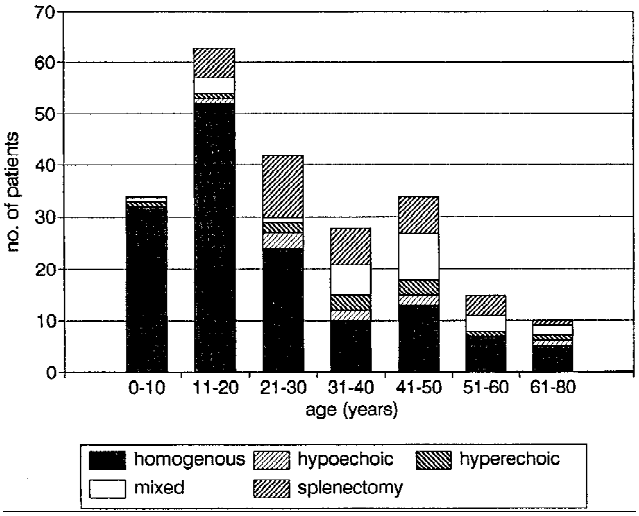

Fig. 2. Texture of the spleen according to age.

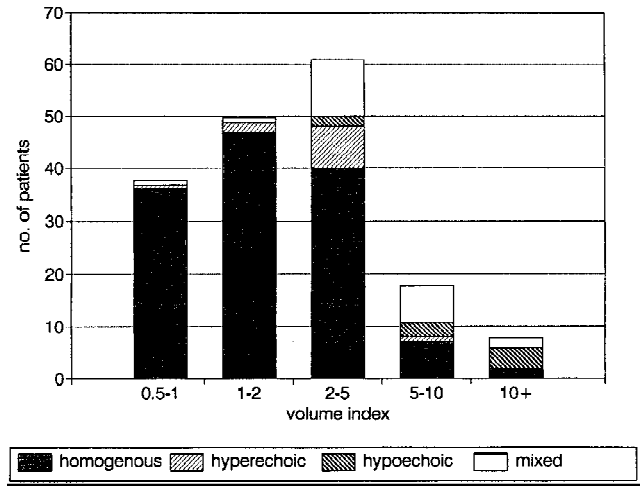

Fig. 3. Texture of spleen according to splenic volume.

an ATL scanner HDI Ultramark 9 and were carried out by one radiologist (I.H.H.). Gaucher disease was confirmed in all patients by enzyme assay and molecular analysis. There were 218 patients of whom 105 were males (48.2%) and 113 were females; 88 patients (40.4%) were under the age of 20 (age range: 2 to 76) years. Thirty-four patients had been splenectomized (15.6%); six patients (2.8%) had partial splenectomies and were included in the non-splenectomized group because they all had experienced re-growth of the splenic remnant.

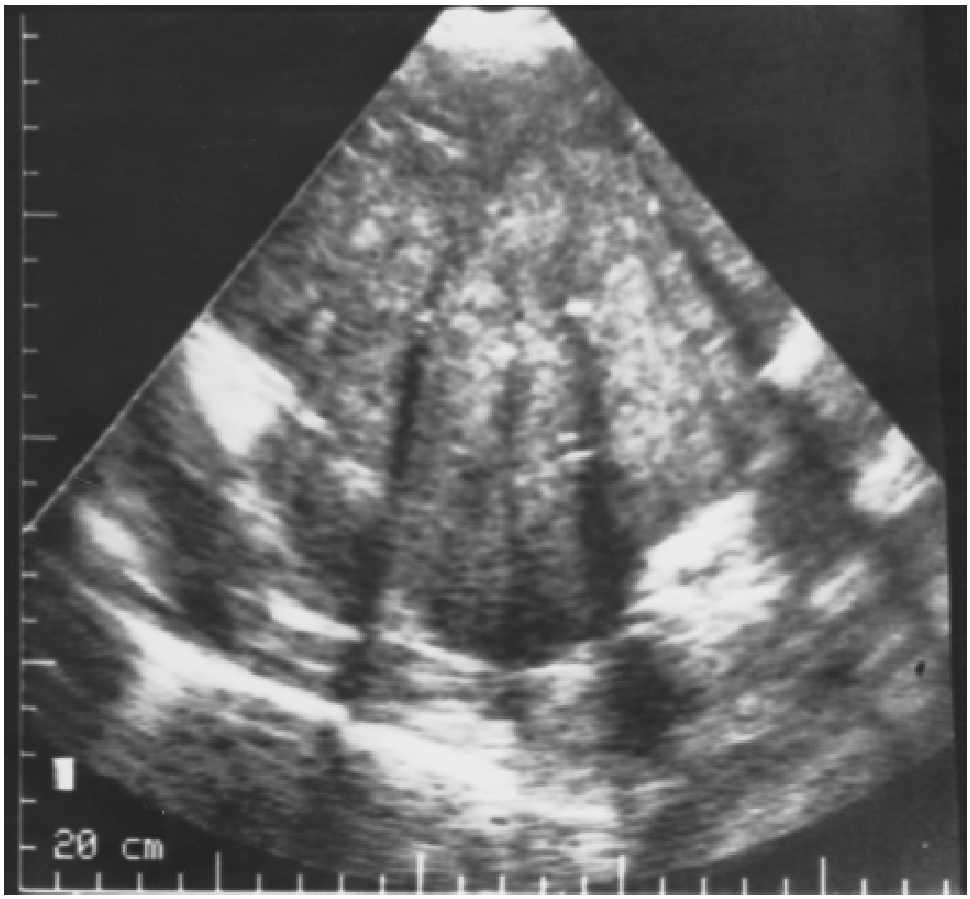

Fig. 4. A sonogram of a re-grown spleen, 8 years after partial splenectomy, demonstrating marked irregularity with multiple calcifications.

Severity score index (SSI), a numerical measure of disease severity based on age at first presentation of symptoms and the extent of spleen, liver, bone, and other organ involvement, was calculated for each patient [7]. In this cohort of patients, the SSI score ranged from 2–29, indicating the full range of mild to severe disease. The most common genotype N370S/N370S (1226G/1226G), which is correlated with clinical mild disease [7], was seen in 109 (50.0%) of the patients.

Statistical analysis included the two sample t-test, which was applied in order to assess the difference between the two spleen texture (homogeneous vs. with lesions) groups, for continuous variables. The association between these two spleen texture groups and other categorical variables was analyzed using the chi-square test.

RESULTS

Splenomegaly was observed in all 184 non-splenectomized patients; in 140 of these (64.2%) the texture of the spleen was homogeneous. In the other 44 patients (20.2%) there were focal lesions: 9 were hypoechoic (4.1%), 12 were hyperechoic (5.5%), and 23 were mixed (10.6%). The lesions were typically well-demarcated from the surrounding parenchyma by smooth borders and ranged in appearance from well-defined, rounded, homogenous to geographic non-homogenous lesions (Fig. 1). In many of these spleens there were multiple lesions with no specific localization; in other patients, there were only a few or solitary lesions.

The presence of lesions correlated with increasing age ($P = 0.0001$) particularly in the 31–40 year period as seen in Figure 2, and with organ enlargement ($P = 0.0001$), particularly in the 5–10 volume index interval as shown in Figure 3, but did not correlate with the extent of bone involvement, genotype, or SSI (data not shown).

In 19 of the 44 patients with lesions (43.2%) who had begun enzyme replacement therapy, there was no change in the appearance of the lesions relative to baseline, despite significant reduction in spleen size on 6 month follow-up ultrasound.

In four of the six patients who had undergone partial splenectomies, the splenic remnant had a coarse texture with multiple calcifications throughout (Fig. 4).

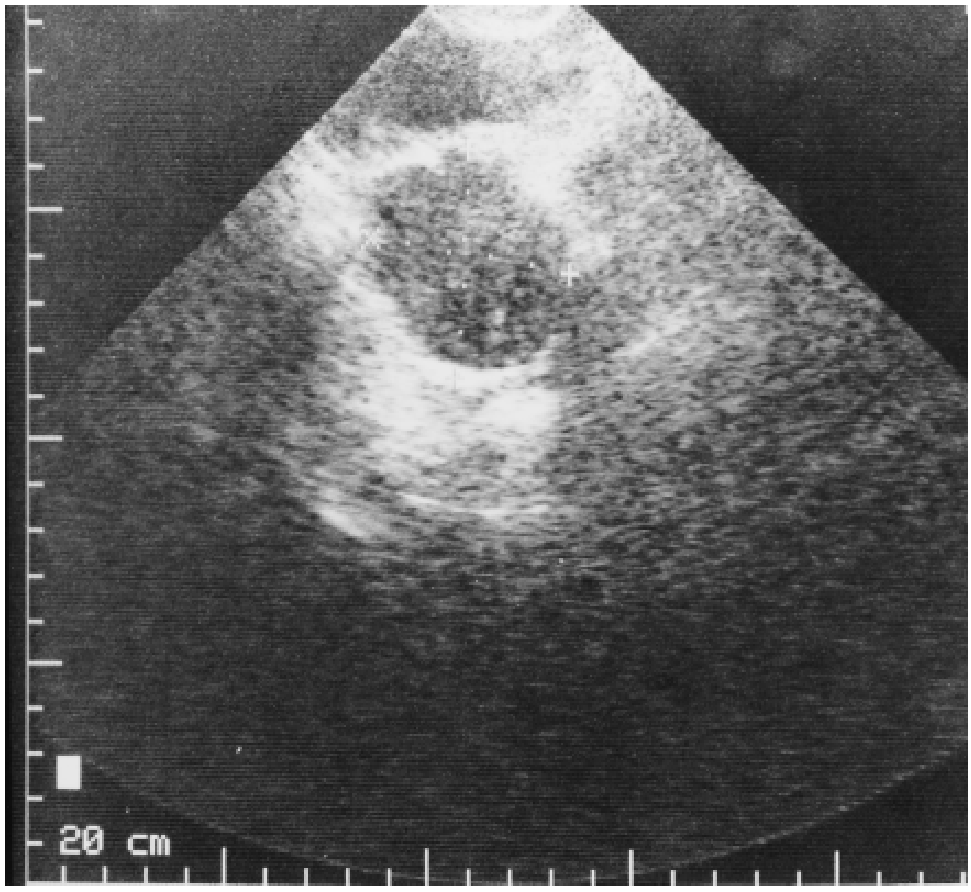

Fig. 5. A relatively enlarged (5 cm × 5 cm × 5 cm) accessory spleen with irregular echogeneity, from a patient with intact spleen.

A total of 36 accessory spleens in 29 patients were evaluated. Only three patients were splenectomized. Eight accessory spleens had focal lesions (22.2%). These accessory spleens tended to be larger than usually observed in the general population; the three largest accessory spleens were encountered in the three splenectomized patients and all these accessory spleens had lesions (Fig. 5).

Hepatomegaly was observed in all splenectomized patients, as well as in 160 (87.0%) of the non-splenectomized patients. There were hepatic lesions in 13 of the total of 218 patients (6.0%), 7 of whom had been splenectomized (53.8%). Five of these patients also had lesions in the spleen (38.5%), and one of these patients had lesions in the accessory spleen (7.7%). The presence of the focal lesions did not correlate with the degree of hepatomegaly. One patient evinced irregular hepatic texture, which was shown on liver biopsy (taken during splenectomy) to be due to cirrhosis probably associated with Gaucher disease.

In 11 of the 34 splenectomized patients (32.4%), significant retroperitoneal and peri-portal lymphadenopathy was demonstrated (Fig. 6). None of the non-splenectomized patients had similar findings.

DISCUSSION

Gaucher patients most often present with symptoms attributable to splenomegaly. Therefore, the universally available, inexpensive, completely non-invasive, as well as radiation-free abdominal sonography, has become a basic diagnostic tool for routine work-up as well as follow-up of all patients. With particular relevance to Gaucher disease, abdominal ultrasound has been found to be an accurate tool for measuring organ volumes as shown in comparisons of the ultrasound index volumes [9] to the calculated volume of the liver by magnetic resonance imaging (MRI) [10], and of the spleen and liver by computerized tomography (CT) (unpublished), and for detecting splenic or hepatic lesions [11]. Similarly, this accuracy has been used for staging of hematological malignancies [12].

The high incidence of splenic lesions detected in our study (20% of 184 non-splenectomized patients) con-

Fig. 6. Abdominal sonogram of a splenectomized Gaucher patient showing retroperitoneal lymphadenopathy.

firms the findings in a previous smaller series of patients (30% of 47), evaluated by both sonography [2] and MRI [8]. Since our data show a clear correlation between the existence of focal splenic lesions with age and with the degree of organomegaly, the most probable explanation for the decreased prevalence in the present series is the wide range of disease severity in our patient population which includes young children, as well as many patients with minimal hepatosplenomegaly.

In the general population, the presence of lesions in the non-traumatized spleen is most often attributable to lymphoma [13]. Sonographically, splenic lymphoma typically shows diffuse or focal hypo-echoic lesions [14, 15], which cannot be radiologically differentiated from the hypoechoic lesions found in patients with Gaucher disease (Fig. 1A). In a study of malignant splenic lesions [11], 71 of 73 were hypoechoic (97.3%) and 2 were hyperechoic (2.7%), whereas in 99 benign lesions, none were hypoechoic and 17 (17.2%) were hyperechoic. Among all our Gaucher patients, 4% had hypoechoic splenic lesions and 11% had mixed splenic lesions. These findings highlight the need to consider Gaucher disease in the differential diagnosis of splenic lesions in Ashkenazi Jewish individuals. Conversely, with the reported increased incidence of hematological malignancies in patients with Gaucher disease [3], it is important to define guidelines for evaluation of these patients for neoplasm when they are found to have focal splenic lesions. In addition, the clinical context is significant, as a Gaucher patient with an enlarged spleen and no other clinical parameters indicative of malignancy who is found to have focal splenic lesions on ultrasound may be followed with imaging studies without a need for invasive procedures to exclude neoplasm. If one or more lesions show a change in character on follow-up ultrasound, complete evaluation is required, as it would be in the case of any onset of new signs or symptoms compatible with cancer. So far, we have not observed ‘‘malignant transformation’’ in any of the intra-splenic or intra-hepatic focal lesions among our Gaucher patients; on the other hand, in two of our patients, the diagnosis of Gaucher disease was secondary to the detection of intra-splenic lesions by ultrasound. Interestingly, in those patients who are treated with enzyme replacement therapy, these lesions are unaffected despite often dramatic decreases in organ size.

Ultrasound has also been an adjunct in assessment of hepatic lesions and diagnosis of hepatic neoplasms [16]. Our series highlights the incidence of lesions of the liver

(6% of 218), more than half of which occurred in splenectomized patients, a finding which was not noted in the previous studies [2,8].

In a study of 64 hepatic lesions discovered during organ imaging in asymptomatic patients [17], 17 (26.6%) were diagnosed as a neoplasm, 11 being malignant (17.2%). In that study it was emphasized that there were no reliable clinical or laboratory data to distinguish between malignant and benign hepatic lesions, although patient age above 55 years, hepatomegaly and elevated alkaline phosphatase were significant risk factors. All three of these risk factors were present in all those whose hepatic lesions were malignant. All of our Gaucher patients who had hepatic lesions had the latter two risk factors of hepatomegaly and elevated alkaline phosphatase levels, but none was over the age of 50 years and none proved to have malignant disease. Thus, Gaucher disease should be included in the differential diagnosis of these lesions.

The presence of lymphadenopathy in nearly one third of our splenectomized Gaucher patients, but in none of the non-splenectomized patients, reported here for the first time, is noteworthy and should be considered in the differential diagnosis of suspected malignancies.

CONCLUSIONS

The finding of a high incidence of both splenic and hepatic lesions in Gaucher patients, including those with rather mild symptoms or with a genotype that is not considered predictive of severe disease, implies that Gaucher disease should be included in the differential diagnosis of patients presenting with focal lesions in abdominal ultrasound. In addition, Gaucher patients with splenic and/or hepatic lesions should be routinely monitored to rule out the possibility of neoplasm, because of the reported increased risk for cancers.

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